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Yoon S. Cho-Chung

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EXAMINER

UNGAR, SUSAN NMN

ART UNIT

PAPER NUMBER

1642

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/018,396	YOON S. CHO-CHUNG	
	<b>Examiner</b>	<b>Art Unit</b>	
	Susan Ungar	1642	

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on 01 May 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☐ Claim(s) 1-8 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) 1-8 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's Declaration and other submissions filed on May 1, 2006 are acknowledged and have been entered. An action on the RCE follows.

2. Claims 1-8 are pending and currently under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. It is noted that claim 1 is drawn to a method of diagnosing cancer in a patient comprising assaying a sample from said patient for ECPKA wherein the presence of an elevated level of ECPKA compared to the level of ECPKA in a control sample is indicative of cancer in said patient (claim 1). Although claim 1 is a broad generic claim which does not define the type of level of ECPKA being assayed, review of the dependent claims as well as the specification reveals that the claims are drawn to two inventions. The claims, in fact are drawn to diagnosis of cancer by (1) assay of enzyme activity level of ECPKA, (2) assay of protein ECPKA level. For clarity, the inventions will be dealt with in two separate rejections under 35 USC 112, first paragraph, one for the diagnosis of cancer by assay of enzyme level of ECPKA and the other for the diagnosis of cancer by assay of protein level of ECPKA.

Further, in the interests of clarity, the rejections set forth below are hereby summarized:

(1) Claims 1-6 are rejected under 35 USC 112, first paragraph as failing to comply with the enablement requirement for the reasons set forth below, that is, the claims are not enabled for the diagnosis of cancer by assay of ECPKA enzyme levels.

(2) If Applicant were able to overcome the rejection set forth above, Claims 1-6 would still be rejected under 35 USC 112, first paragraph as failing to comply with the scope enablement requirement for the reasons set forth below, that is the claims are not enabled for the scope of the claimed invention drawn to “increased levels” of enzyme activity.

(3) Claims 1, 2, 4, 5, 7-8 are rejected under 35 USC 112, first paragraph as failing to comply with the enablement requirement for the reasons set forth below, that is, the claims are not enabled for the diagnosis of cancer by assay of ECPKA protein levels.

(4) If Applicant were able to overcome the rejection set forth above, Claims 1, 2, 4, 5, 7-8 would still be rejected under 35 USC 112, first paragraph as failing to comply with the scope enablement requirement for the reasons set forth below, that is the claims are not enabled for the scope of the claimed invention drawn to assay of ECPKA protein levels by assay of enzyme activity.

(5) If Applicant were able to overcome the rejection set forth above, Claim 4 would still be rejected under 35 USC 112, first paragraph as failing to comply with the scope enablement requirement for the reasons set forth below, that is the claims are not enabled for the scope of the claimed invention drawn to diagnosis of specific cancers.

(6) If Applicant were able to overcome the rejection set forth above, Claim 7 would still be rejected under 35 USC 112, first paragraph as failing to comply with

the scope enablement requirement for the reasons set forth below, that is that the claims are not enabled for the scope of the claimed invention drawn to ELISA.

(7) Claims 1-8 are rejected under 35 USC 112, second paragraph as being indefinite, that is the claims are indefinite in the use of the phrase "increased level" and the claims are indefinite in the omission of a critical element.

### **New Grounds of Rejection**

#### **Claim Rejections - 35 USC 112**

4. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of diagnosing cancer in a patient comprising assaying a sample from said patient for ECPKA enzyme activity wherein the presence of an elevated level of ECPKA, compared to the level of ECPKA, in a control sample is indicative of cancer in said patient, wherein the activity level of ECPKA enzyme activity in said control sample is from about 0 to about 1.0 mUnits/ml blood serum.

The specification teaches that the present invention provides a method of diagnosing cancer in a patient comprising assaying for the presence of ECPKA (p. 1). The specification teaches the detection of ECPKA in serum samples of cancer patients by assay of ECPKA enzyme activity using the conventional Kemptide PKA activity assay (p. 22). The specification teaches that ECPKA activity was significantly elevated in the serum samples from cancer patients compared to that in normal serum samples (p. 34). The specification also teaches that "Preferably,

the control sample is in a similar format, measurement and units as the patient sample. For instance, a suitable control is one that is produced from the same biological material using techniques similar to those that are used to generate the patient sample. In this regard, the level of ECPKA in a control sample **IS** (emphasis added) from about 0 to about 1.0 mUnits/ml blood serum or urine (p. 9). Further, the claims as currently constituted claim that the “activity level of ECPKA in said control sample is from about 0 to about 1.0 mUnits/ml blood serum” (claims 3 and 6).

One cannot extrapolate the teaching of the specification to the enablement of the claims because Applicant teaches that the level of ECPKA activity was significantly elevated in the serum samples from cancer patients compared to that in normal control and not only teaches but claims that the level of ECPKA activity in a control sample **IS** from about 0 to about 1.0 mUnits/ml blood serum. However the inventor of the instant invention teaches, in WO2005/088312 (a six year post filing reference), that assay of 66 normal controls revealed that the mean value of ECPKA activity in the serum of normal controls was 60 mU/ml of serum (p. 22), wherein the enzyme activity assay was the conventional Kemptide PKA activity assay (p. 21). Thus, it is clear that the same inventor, using the same Kemptide assay found an average ECPKA activity in normal controls that was sixty times the control level taught and claimed by the instant inventor in the instant application. Given the teachings of WO2005/088312, no one of ordinary skill in the art would find it more likely than not that the instantly claimed invention could be used to predictably distinguish between those patients who have cancer and those that did not by the presence of an elevated level of ECPKA activity in said sample compared to the level of ECPKA in a control sample wherein the specification

teaches and claims that the level of ECPKA activity in a control sample IS from about 0 to about 1.0 mUnits/ml blood serum, with a reasonable expectation of success because it is clear that almost every normal patient assayed in the 2005 patient would be improperly diagnosed as having cancer.

The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention as currently claimed would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

6. If Applicant were able to overcome the rejection under 35 USC 112, first paragraph above, Claims 1-6 would still be rejected under 35 USC 112, first paragraph because while being enabling for a method of diagnosing cancer in a patient comprising assaying a sample from said patient for ECPKA enzyme activity wherein the presence of a level of ECPKA enzyme activity above a specified cut-off point compared to the level of ECPKA enzyme activity in a control sample is indicative of cancer in said patient, does not reasonably provide enablement for the claimed method wherein the presence of an elevated level of ECPKA in said sample compared to the level of ECPKA in a control sample is indicative of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to a method of diagnosing cancer in a patient comprising assaying a sample from said patient for ECPKA enzyme activity

wherein the presence of an elevated level of ECPKA compared to the level of ECPKA in a control sample is indicative of cancer in said patient.

The specification teaches as set forth above, that is the present invention provides a method of diagnosing cancer in a patient comprising assaying for the presence of ECPKA (p. 1). The specification teaches the detection of ECPKA in serum samples of cancer patients by assay of PKA enzyme activity using the conventional Kemptide PKA activity assay (p. 22). The specification teaches that ECPKA activity was significantly elevated in the serum samples from cancer patients compared to that in normal serum samples (p. 34).

One cannot extrapolate the teaching of the specification to the scope of the claims because Applicant teaches that the level of ECPKA activity was significantly elevated in the serum samples from cancer patients compared to that in normal control and therefore the cancer patients were distinguishable from the non-cancer patients. However Cho-Chung, the inventor of the instant invention teaches, in WO2005/088312 (a six year post filing reference), that there is considerable overlap in ECPKA enzyme activity between cancer patients and normal controls and therefore that assay of ECPKA enzymatic activity for the diagnosis of cancer lacks both sensitivity and specificity (p.22). It is noted that Cho-Chung also teaches methods of establishing appropriate cut-off values for the sensitivity and specificity of diagnosis of cancer using ROC curves (p. 21). Given the teaching drawn to the lack of sensitivity and specificity of the instantly claimed assay, it is clear that the establishment of a cut-off point is critical to the ability of one of ordinary skill to use the claimed method with a reasonable expectation of success. For Applicant's information, as drawn to the cut-off point, Stites et al (Basic and Clinical Immunology, 7th Ed, Appleton and Lange, Norwalk, 1991,

page 260) specifically teaches that when any diagnostic test is used to make a decision, there is some probability of drawing an erroneous conclusion and that predictive value theory can be used to deal with this problem. The reference further teaches that diagnostic sensitivity is defined as the fraction of diseased subjects with abnormal test results and that diagnostic specificity is defined as the fraction of nondiseased subjects who have a normal laboratory test. Further, Stites et al teach that the positive predictive value is the fraction of abnormal tests that represent disease and the negative predictive value is the fraction of normal tests that represent the absence of disease (p. 260, col 1). Stites et al specifically teach that diagnostic sensitivity and specificity reveal something about the test *given prior knowledge about the disease status* (emphasis in the original document), whereas positive and negative predictive values *estimate the likelihood of disease given the test result* (emphasis in the original document). Clearly it is the latter case that is of interest when trying to make a diagnosis (p. 260, para bridging cols 1 and 2).

Given the art recognized overlap of enzyme activity in both cancer and control patients, given Inventor Cho-Chung's statements drawn to the lack of sensitivity and specificity of the instantly claimed invention, in the absence of a cut-off point that could be used with a reasonable expectation of success to distinguish between those patients who have cancer from those that do not, the claimed invention is not enabled. Clearly, it would be expected, given both the information in the specification as originally filed and the information now known in the art, that the use of the instant invention would lead to a substantial number of the patients who have cancer who would be determined to be cancer free as well as to a substantial number of the patients who do not have cancer to have the

disease would be to be determined to have cancer. The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention as currently claimed would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. Claims 1, 2, 4, 5, 7-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of diagnosing cancer in a patient comprising assaying a sample from said patient for ECPKA protein level wherein the presence of an elevated level of ECPKA protein level compared to the level of ECPKA in a control sample is indicative of cancer in said patient.

The specification teaches that the present invention provides a method of diagnosing cancer in a patient comprising assaying for the presence of ECPKA (p. 1). The specification exemplifies increased PKA activity in conditioned medium from cancer cell lines and in serum from cancer patients (see Examples 1, 7). The specification hypothesizes that expression of ECPKA is regulated by intracellular PKA and exemplifies increases in ECPKA enzyme activity, both in cell extract and conditioned medium from cells that have been transfected with, and that constitutively express, one or both of the C and R subunits of PKA (Example 5, p. 25-29). Both Example 1 and Example 6 disclose assays for protein concentration, however, neither Example discloses that protein concentration of ECPKA was

determined and no data drawn to ECPKA protein concentration is found in the specification. It is noted that Cho-Chung, the inventor of the instantly claimed inventor, in WO2005/088312, equates enzyme activity with protein concentration when he states that "ECPKA enzymatic assay (which measures antigen concentration) gives a significant overlap between cancer patients.....and normal controls.....".

One cannot extrapolate the teaching of the specification to the enablement of the claims because Cho-Chung, WO2005/088312 (a six year post filing reference) equates ECPKA enzyme activity and antigen concentration and teaches that there is considerable overlap in ECPKA enzyme activity between cancer patients and normal controls and therefore that assay of ECPKA enzymatic activity for the diagnosis of cancer lacks both sensitivity and specificity (p.22). The correlary of this teaching is that there is considerable overlap of antigen concentration between cancer patients and normal control and thus the antigen concentration, as drawn to the diagnosis of cancer, lacks sensitivity and specificity. If one were to accept the hypothesis that ECPKA antigen concentration could be predictably determined by enzyme activity assay, it is clear that given the teaching of Cho-Chung WO2005/08813, there would be significant overlap between ECPKA protein levels in cancer patients and normal controls. However, Applicant's arguments in the paper submitted May 1, 2006 call into serious question the apparent hypothesis that ECPKA enzyme levels could be used to predictably determine protein levels with a reasonable expectation of success. In particular, Applicant argues that autoantibodies to extracellular PKA can be used as a basis to detect cancer and that since autoantibodies are generated in response to the introduction of antigen into the serum, these results demonstrate that extra-cellular PKA serum protein levels

are enhanced in cancer patients and Applicant points to Cho-Chung, WO2005/088312. However, Cho-Chung, WO2005/088312 specifically teaches that there is no correlation between the titers of anti-ECPKA IgG antibody obtained by ELISA and ECPKA measured by enzymatic assay. Given Applicant's arguments and the teachings of Cho-Chung, WO2005/088312, it appears that ECPKA enzymatic activity **IS NOT** indicative of protein levels since there is **no correlation** between the titers of anti-ECPKA IgG antibody obtained by ELISA and ECPKA measured by enzymatic assay.

Further, those of ordinary skill in the art recognize that deregulation of protein kinases, that is increases in their activity, is associated with cancer phenotypes. However, those increases in activity are not limited to elevated levels of catalytic enzyme subunits. A wide variety of alterations in the enzymes, their cofactors and effectors lead to unregulated activity and are known in the art. For example, SRC, a protein kinase, is mutated in a subset of advanced human colon cancers. This mutation eliminates a phosphorylation site that regulates enzyme activity, is activating, transforming, tumorigenic and promotes metastasis and results in high enzyme activity in colon cancer patients compared with normal control (see Irby et al, Nature Genetics, 1999, 21:187-190, abstract, of record). Further, CDK4, a protein kinase, is mutated in a subset of melanoma patients. CDK4 binding with protein cyclin D promote the passage of cells through the G1 checkpoint. This activity is regulated by protein p16. p16 controls cell growth by inhibiting the activity of the CDK4-cyclin D complex and stopping cells at the G1 checkpoint. The CDK4 mutation disrupts the cell growth-inhibiting effects of p16 by preventing p16 from binding to CDK4 at the G1 checkpoint. Further, in a subset of melanoma patients it was found that p16 is mutated, preventing the

encoded protein from exerting its regulatory effects on the CDK4 complex (see CDK4 identified as a Familial Melanoma Gene downloaded from <http://www.skincancer.org/melanoma/cdk4.php>, of record which reports the findings of Wolfel et al, Science, 1995, 269:1281-1284 and Zuo et al, Nature Genetics, 1996, 12:97-99), of record. In addition, Stott et al (BioTeach, Oncogenes: The (Autosomal Dominant Evil) downloaded from <http://www.bioteach.ubc.ca/Cell Biology/Oncogenes/>), of record specifically teaches the range of mutations that can occur that lead to the transformation of from proto-oncogenes to oncogenes. In particular, the reference teaches that Abl is a tyrosine kinase that requires cytokine stimulation to be activated. In its monomeric form Abl is inactive. When cytokines are present, two monomers auto-phosphorylate, resulting in activation. Conversely, the bcr gene contains a dimerization motif, but no kinase activity. When a translocation occurs between the abl gene and the rc gene, the fusion product contains the dimerization domain of Bcr and the kinase domain of Abl. Consequently, the fusion protein dimerizes in the absence of cytokine, resulting in a constitutively active tyrosine kinase and uncontrolled cell division. Thus, it is clear that cellular events other than elevated levels are known to be responsible for increases of protein kinase activity. Further, it is also reasonable to conjecture that the increased enzyme activity found in the serum of cancer patients could be caused as well by cancer-dependent decreases in the affinity of the R and C subunits, increased affinity for substrate, cancer-dependent increases in extracellular camp. Although Applicant hypothesizes that exemplified increased activity of ECPKA in serum of cancer patients is due to increased expression of one or both of the subunits of ECPKA, given the above, based on the information in the specification, and known in the art at the time the

invention was made, it is just as reasonable to hypothesize that the increased activity demonstrated in the serum of cancer patients is due to alteration of sites associated with allosteric effectors, reduced availability of inhibitor, reduced affinity for inhibitor, mutation of the catalytic subunit that leads to constitutive activation, altered affinity for regulatory subunit, altered affinity for substrate.

The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention as currently claimed would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Some of Applicant's arguments drawn to the rejection of claims 1-8 in the paper mailed November 1, 2005, Section 4, pages 2-9 are relevant to the instant rejection of claims 1-6.

Applicant argues that the Office presents no evidence that PKA enzyme activity is influenced by any of the factors mentioned. The argument has been considered but has not been found persuasive because, although the evidence presented is not drawn specifically to PKA, the evidence presented is drawn to the family of proteins to which PKA belongs, that is, it is drawn to the deregulation of protein kinases by a wide variety of alterations in the enzymes, their cofactors and effectors wherein Examiner presents evidence drawn to SRC, CDK4, abl, all members of the protein kinase family with different structures, functions, cofactors and effectors. Given the broad range of family members that are deregulated by factors other than elevated levels, given that protein concentrations are not directly assayed in the instant specification or in the art of record, given the information

known in the art drawn to cancer associated alterations in enzyme activity, given the clear teaching in WO2005/088312 of the overlap of ECPKA protein between cancer patients and normal controls, given Applicant's arguments that autoantibodies demonstrate that extra-cellular PKA serum protein levels are enhanced in cancer patients, given that there is no correlation between enzyme activity and autoantibody levels, one of ordinary skill in the art would not believe that it is more likely than not that the increased enzyme activity demonstrated in serum of cancer patients is caused by elevated levels/differential expression of ECPKA in cancer patients compared to normal control. Finally, it is noted that although Applicant argues that insufficient evidence is provided, Applicant does not state that the Office is incorrect in its findings.

Applicant argues that the Office completely ignores the substantial evidence presented in the application that shows extra-cellular PKA activity is linked to increased expression and points to Example 1 wherein PKA activity in the conditioned medium of cancer cells is demonstrated. The argument has been considered but has not been found persuasive because although a review of example 1 revealed that the presence of PKA activity in conditioned medium is identified, there is no teaching that the activity is linked to increased expression of PKA as no normal cells of the same tissue type were assayed. This is of critical importance given the teaching of Cho-Chung, WO2005/088312, Supra, that not only cancer cells, but normal cell systems present with PKA activity in serum. Applicant is invited to submit objective evidence demonstrating a nexus between differential extracellular PKA enzyme activity and protein expression in cancer patients compared to normal controls in order to obviate this grounds of rejection.

Applicant further argues that Example 5 shows that increased extra-cellular PKA enzyme activity is tied to increased intracellular expression of PKA. The argument has been considered but has not been found persuasive because Example 5 is drawn to an *in vitro* assay wherein PC3M cells were transfected with the Calpha and R subunits of PKA wherein constitutive expression of subunit(s) resulted in increased extracellular activity. As previously set forth, this model is not commensurate in scope with the claimed invention and therefore does not support the enablement of the instantly claimed invention. Applicant is invited to submit objective evidence demonstrating a nexus between differential extracellular PKA enzyme activity and protein expression in cancer patients compared to normal controls in order to obviate this grounds of rejection.

Applicant argues that autoantibodies to extracellular PKA can be used as a basis to detect cancer and that since autoantibodies are generated in response to the introduction of antigen into the serum, these results demonstrate that extra-cellular PKA serum protein levels are enhanced in cancer patients and Applicant points to Cho-Chung, WO2005/088312. The argument has been considered but have not been found persuasive because a review of Cho-Chung, WO2005/088312 reveals that the assays found autoantibodies to ECPKA in not only the serum of cancer patients but also in the serum of normal controls (p. 21). Further, Cho-Chung, WO2005/088312 teach that there is no correlation between the titers of anti-ECPKA IgG antibody obtained by ELISA and ECPKA measured by enzymatic assay. Given Applicant's arguments and the teachings of Cho-Chung, WO2005/088312, it is clear that PKA enzymatic activity **is not** indicative of protein levels since there is **no correlation** between the titers of anti-ECPKA IgG antibody obtained by ELISA and ECPKA measured by enzymatic assay. On the

other hand, if one were to assume, as does Applicant, that the PKA enzymatic activity is indicative of protein levels, it is clear that the titers of autoantibody ARE NOT indicative of protein levels, therefore contrary to Applicant's arguments, the presence of autoantibodies does not demonstrate enhanced serum PKA protein levels in cancer patients. Given Applicant's apparent confusion as to what parameter is appropriate to identify protein levels in serum, given the clear understanding in the art that factors other than elevated levels of protein are known to alter enzyme activity of members of the protein kinase family, it is clear that in the absence of objective evidence demonstrating differential protein in serum between cancer patients and normal controls, one could not predict that in fact PKA protein level in the serum of cancer patients is different from that of normal control.

Applicant further argues that Mani et al reports that extracellular PKA protein levels in the serum of cancer patients have been used as a basis to track patient responses to various cancer treatments in clinical trials. The argument has been considered but has not been found persuasive because a review of Mani et al reveals that although Mani et al report both western blot analysis and enzymatic analysis of ECPKA in serum of patients, the reference presents no data drawn to the western blot analysis other than to state that treatment led to markedly decreased levels of ECPKA activity and a decline in C alpha abundance. The reference does not define the term "decline", does not state whether the decline is useful for distinguishing between those patients that have cancer and those that do not, does not disclose the abundance of ECPKA protein in normal patients. Given the above, the information in the Mani et al reference, drawn to enzyme activity and protein abundance cannot be evaluated. However, the reference goes on to

state that the protein assay requires validation and standardization for clinical use (see page 257). This statement in Mani et al, drawn to the requirement for validation of protein assay for clinical use in a reference published 4 years post filing of the instant application, once again seriously raises a question as to the enablement of the instantly claimed assay and its ability to be used with a reasonable expectation of success.

Given that Inventor Cho-Chung is an author of the Mani et al reference, Applicant is invited to submit objective evidence demonstrating a nexus between differential extracellular PKA activity in serum and protein level in serum from cancer patients compared to normal controls so that the information in the Mani reference can be evaluated.

Applicant further points to Lockhart et al and states that the reference discloses that ECPKA serum levels have been used as a basis to track the response of cancer patients. The argument has been considered but has not been found persuasive because the reference is drawn to the measurement of enzyme activity and is not drawn to protein level. Further, no normal control is presented so that even the enzyme activity data presented cannot be evaluated, especially given the teaching of Cho-Chung, WO2005/088312 drawn to ECPKA enzyme activity in normal controls.

The arguments have been carefully considered but have not been found persuasive.

8. If Applicant were able to overcome the rejections under 35 USC 112, first paragraph above, Claims 1, 2, 4, 5, 7-8 would still be rejected under 35 USC 112, first paragraph because while being enabling for a method of diagnosing cancer in a patient comprising assaying a sample from said patient for ECPKA protein level

wherein the presence of a level of ECPKA protein level above a specified cut-off point compared to the level of ECPKA protein level in a control sample is indicative of cancer in said patient, does not reasonably provide enablement for the claimed method wherein the presence of an elevated level of ECPKA in said sample compared to the level of ECPKA in a control sample is indicative of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Given the teachings of Cho-Chung, WO2005/088312 drawn to the equivalence of ECPKA enzyme activity and antigen concentration as well as the lack of information in the specification drawn to direct assay of ECPKA protein, it is assumed for examination purposes that enzyme activity of ECPKA is equivalent to antigen concentration for the purposes of this rejection of claims 1, 2, 4, 5, 7-8 under the scope provisions of 35 USC 112, first paragraph.

The claims are drawn to a method of diagnosing cancer in a patient comprising assaying a sample from said patient for ECPKA protein level wherein the presence of an elevated level of ECPKA compared to the level of ECPKA in a control sample is indicative of cancer in said patient.

The specification teaches that the present invention provides a method of diagnosing cancer in a patient comprising assaying for the presence of ECPKA (p. 1). The specification teaches the detection of ECPKA in conditioned medium of cultured cancer cells by assay of PKA enzyme activity (p. 21) as well as the detection of ECPKA in serum samples of cancer patients wherein said samples were assayed for ECPKA activity using the conventional Kemptide PKA activity assay (p. 22). The specification teaches that ECPKA activity was significantly

elevated in the serum samples from cancer patients compared to that in normal serum samples (p. 34). The specification hypothesizes that expression of ECPKA is regulated by intracellular PKA and exemplifies increases in ECPKA enzyme activity, both in cell extract and conditioned medium from cells that have been transfected with, and that constitutively express, one or both of the C and R subunits of PKA (Example 5, p. 25-29). It is noted that Cho-Chung, the inventor of the instantly claimed inventor, in WO2005/088312 equates enzyme activity with protein concentration when he states that "ECPKA enzymatic assay (which measures antigen concentration) gives a significant overlap between cancer patients.....and normal controls.....".

One cannot extrapolate the teaching of the specification to the scope of the claims because Cho-Chung, WO2005/088312 teaches that there is considerable overlap in ECPKA enzyme activity between cancer patients and normal controls and therefore that assay of ECPKA enzymatic activity for the diagnosis of cancer lacks both sensitivity and specificity (p.22). Given this teaching and the equivalence of protein concentration level to enzyme activity level, it is clear that there is considerable overlap in ECPKA protein level between cancer patients and normal controls. It is once again noted that Cho-Chung also teaches methods of establishing appropriate cut-off values for the sensitivity and specificity of diagnosis of cancer using ROC curves (p. 21). Given the art recognized overlap of protein concentration level between cancer patients and normal controls, given the teaching drawn to the lack of sensitivity and specificity of the instantly claimed assay, it is clear that the establishment of a cut-off point is critical to the ability of one of ordinary skill to use the claimed assay with a reasonable expectation of success, that is to reliably and predictably distinguish between those patients who

have cancer from those that do not. It would be expected, given both the information in the specification as originally filed and the information now known in the art, that the use of the instant invention would lead to a substantial number of the patients who have cancer to be determined cancer free as well as to a substantial number of the patients who do not have cancer to have the disease to be determined to have cancer. The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention as currently claimed would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

9. If applicant were able to overcome the rejections set forth above, claim 4 would still be rejected under 35 USC 112, first paragraph because the specification, while enabling for diagnosing the specific cancers claimed in claim 4 wherein the method includes the steps of assaying for well known genetic or protein markers which are predictive of a particular cancer, does not reasonably provide enablement for the claimed method wherein the presence of an elevated level of ECPKA in said sample compared to the level of ECPKA in a control sample is indicative of cancer the specifically claimed cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claim is drawn to the specific diagnosis of breast cancer, prostate cancer, ovarian cancer, colon cancer, pancreatic cancer, lung cancer, or bladder cancer by assaying for ECPKA level. This means that the claims are drawn

to the diagnosis of specific cancers by assaying for a marker found in a broad variety of cancers.

The specification teaches that ECPKA activity was significantly elevated in the serum samples from cancer patients compared to that in normal serum samples (p. 34). The specification also teaches that the specific type of cancer detected by the presence of ECPKA can be subsequently or simultaneously determined by methods well-known in the art and teaches well known genetic or protein markers which are predictive of a particular cancer.

One cannot extrapolate the teaching of the specification to the scope of the claims because it is clear, that in the absence of additional tests, it is not possible to determine any specific cancer. It appears that the additional tests are critical to the instantly claimed invention. Although the specification teaches that the specific type of cancer detected by the presence of ECPKA can be subsequently or simultaneously determined by methods well-known in the art and teaches well known genetic or protein markers which are predictive of a particular cancer, the claims as currently constituted do not recite method steps drawn to the identification of a particular cancer. It is noted that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Guens , 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, even if it were to be found that the novel ECPKA is overexpressed in serum of cancer patients and that the increased phosphorylation activity exemplified in the specification is associated with increased expression of PKA subunits, given that the specification clearly exemplifies the increased phosphorylation in serum over a broad range of cancer types one could not, in the absence of method steps drawn to identification of a particular cancer, distinguish

between cancer types and practice the invention as currently constituted with a reasonable expectation of success.

10. If Applicant were able to overcome the rejections set forth above, claim 7 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for ELISA comprising the use of an antibody to the catalytic subunit of ECPKA, does not reasonably provide enablement for said method which involves the use of ELISA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are drawn to assaying for ECPKA by the use of ELISA. This means assay by antibody to Calpha, R subunit of ECPKA as well as antibody that distinguishes between ECPKA and intracellular PKA.

The specification teaches and originally claimed using antibody to the catalytic subunit and the regulatory subunit of ECPKA for determining the concentration of ECPKA. Further, the specification teaches that a monoclonal antibody that distinguishes ECPKA from intracellular PKA and ectoPKA can be generated in accordance with methods known in the art (p. 20, lines 25-28).

One cannot extrapolate the teaching of the specification to the scope of the claims because the specification as originally filed teaches that ECPKA in human sera was present in the active free C subunit form (p. 35), a teaching corroborated by Cho-Chung et al, PNAS, of record. Thus, it is clear that the concentration of ECPKA cannot be determined by using ELISA with antibody to the regulatory subunit of ECPKA. Further, Cho et al, PNAS, of record specifically teaches that ECPKA is immunologically and biochemically identical to the intracellular PKA catalytic subunit Calpha (p. 839, col 2). Thus it is clear that antibody that

distinguishes ECPKA from intracellular PKA and ectoPKA cannot be used in the assay, because it is clear that from the post filing reference that, contrary to Applicant's teaching, a distinguishing antibody cannot be made.

The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention as currently claimed would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

11. Claims 1-8 are indefinite because claim 1 recites the phrase "an elevated level of ECPKA". The phrase is indefinite because the term "elevated" is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 4 is indefinite because the method is missing a critical element. The critical element is the additional step of assaying for a specific cancer type.

12. No claims allowed.

13. All other objections and rejections set forth in the previous office action are hereby withdrawn.

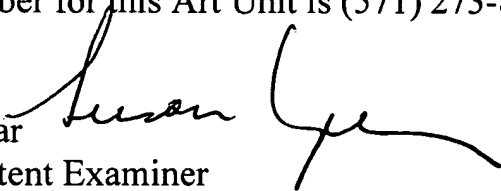
14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Susan Ungar  
Primary Patent Examiner  
August 23, 2006

A handwritten signature in black ink, appearing to read 'Susan Ungar', is written over the printed name and title.